Direct Vinylogous Aldol Reaction Triggered by Tetrabutylammonium Fluoride: A Highly Regioselective and Diastereoselective Addition of Cyclic β-Haloenals to Aromatic Aldehydes

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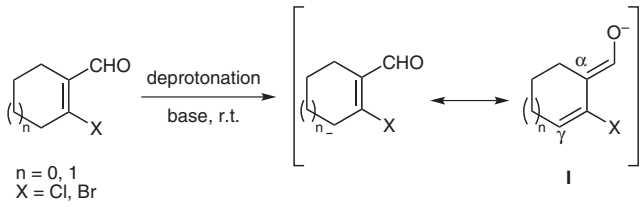
Abstract: A new type of direct vinylogous aldol addition between cyclic β-haloenals and aromatic aldehydes promoted by TBAF has been developed. The reaction was carried out under mild conditions to provide highly functionalized δ-hydroxy-β-halo-α,β-unsaturated aldehydes with high diastereomeric ratios and low to good yields.

Key words: direct vinylogous aldol reaction, TBAF, cyclic β-haloenals, regio- and diastereoselectivity, homoallylic alcohols

Vinylogous aldol (VA) reactions of dienolates have been intensively investigated due to their application in the synthesis of natural products and biologically active compounds.[1,2] Generally, a γ-enolizable α,β-unsaturated carbonyl compound can be used as a precursor of nucleophilic dienolate equivalent in a VA addition to give δ-hydroxy-α,β-unsaturated carbonyl compounds in which up to two stereocenters and one double bond can be created simultaneously.[1b]

However, the VA reaction offers the challenges of site selectivity and the already present issues of stereoselectivity. It has been a particular field of research for synthetic chemists. Addition of a dienolate to an aldehyde has the possibility to afford a mixture of both α- and γ-addition products. A common method that allows for γ-site selectivity is the use of preformed, stable dienolate equivalents, which have been successfully applied to vinylogous Mukaiyama aldol (VMA) reactions.[3] Alternatively, the direct VA reaction was performed on the unmodified γ-enolizable α,β-unsaturated carbonyl compounds by strong-base-induced generation of the dienolates in situ, which provides a practical entry to highly functionalized δ-hydroxy carbonyl compounds and avoids the stoichiometric preactivation of the vinylogous nucleophilic components. For example, both direct VA[4] and asymmetric direct VA[5] additions between furanone or pyrrolinone systems and carbonyl compounds to construct butenolide-related molecular fragments have been thoroughly studied in recent years. A direct vinylogous nitroaldol reaction using nitroisoxazole was also reported by Adamo.[6] In addition, three cases in the acyclic direct VA reactions are worth mentioning: two pertaining to the use of allenyl enolates or alkynylenolates,[7] and another involving heterocyclic magnesium dienolates.[8]

Indeed, examples of direct VA reactions are rare despite their distinct advantages of being more atom-economical and ecologically friendly. Especially, converting an α,β-unsaturated aldehyde into a dienolate, which served as nucleophile in the direct VA addition, has still remained unexplored. Three direct VA reactions of salicylaldehydes with γ-enolizable α,β-unsaturated aldehydes have been reported by Woggon groups and Bräse groups.[9] Additionally, two preceding direct VA reactions involving Yamamoto's remote aldolization technique of α,β-unsaturated aldehyde based on bulky aluminum tris(2,6-diphenylphenoxide) (ATPH) were also studied, which gave a variety of functionalized δ-hydroxy-α,β-unsaturated aldehydes.[10] However, this direct VA reaction required the use of a strong base, such as LDA, and operated at low temperature (–78 °C). Recently, we reported a more simple protocol that starts from a cyclic β-haloenal in the presence of tetrabutylammonium fluoride (TBAF) to generate a cyclic dienolate **I** in situ under mild conditions (Scheme 1).[11]



Scheme 1 A cyclic dienolate generated in situ

By converting an unsaturated aldehyde into a dienolate, this reactive nucleophile **I** which present several possible sites encouraged us to explore the aldol addition of an unsaturated aldehyde to an aldehyde triggered by Lewis/Brønsted bases at room temperature. Two possible pathways for the aldol addition are depicted in Scheme 2, we wondered whether bases could solve the challenge of a direct vinylogous nucleophilic addition of unmodified unsaturated aldehydes.

We initiated our investigation of cyclic β-chloro enal **1a** (0.50 mmol) with an activated aldehyde **2a** (0.65 mmol) in the presence of TBAF (100 mol%) in THF at 25 °C. Interestingly, the reaction mixture was stirred for 22 minutes to give, after chromatography on silica gel, homoallylic al-

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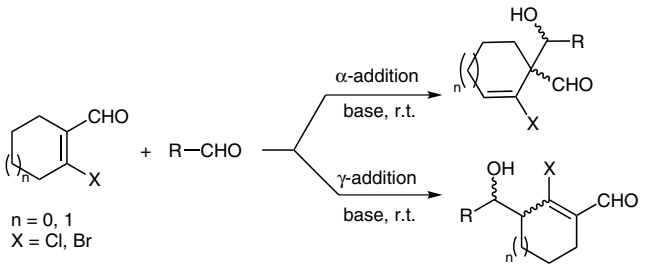
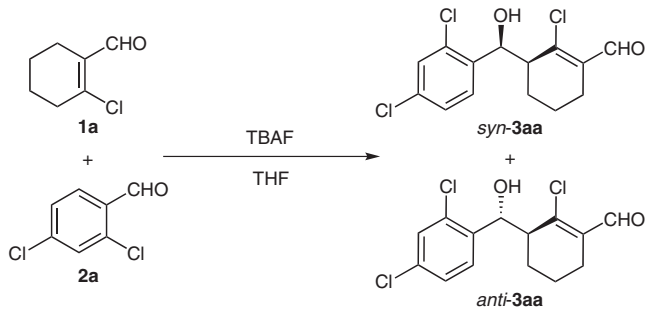


Scheme 2 Two possible pathways for the aldol reaction



Scheme 3 Direct vinylogous aldol addition triggered by TBAF

cohol **3aa** in 57% yield with 97:3 dr detected by ^{1}H NMR spectroscopy (Scheme 3).

It is to be noted that the aldol addition occurred exclusively at the γ-position of β-chloro enal **1a**. The X-ray crystal structure of homoallylic alcohol *syn*-**3aa** is shown in Figure 1.[12]

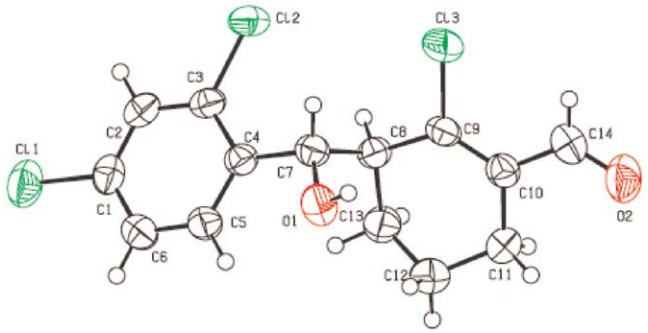


Figure 1 X-ray crystal structure of homoallylic alcohol *syn*-**3aa**

Next, we optimized the reaction conditions for this direct VA addition of the two different aldehydes **1a** and **2a** (Table 1). Firstly, the reaction was carried out by employing different bases to study the effect of basicity on the VA addition. To our disappointment, six organic amine bases (DBU, DABCO, Et_3N, DMAP, imidazole, and quinidine) could not promote the above-mentioned VA reaction at all. This result indicated that TBAF is an effective base in the deprotonation of cyclic β-halo enal **1a** to give the enolate **I** in situ. Four different solvents listed in Table 1 were then tested (Table 1, entries 1–4). Conducting the reaction in DMF gave the same yield as in THF, and a slightly improved diastereomeric ratio (98:2) was achieved. Use of DMSO as the solvent caused a significant increase in the reaction rate and maintained a high level of diastereoselectivity. Acetonitrile compromised the yield and markedly retarded the reaction while exhibiting the highest diastereomeric ratio (99:1). Gratifyingly, lowering the reaction temperature from 25 °C to 18 °C caused an increase in the product yield to 69% after 1.5 minutes (Table 1, entry 5). Upon decreasing the amount of TBAF to 90 mol% at 18 °C, the VA product was obtained in excellent yield with 98:2 dr (Table 1, entry 6). When 80 mol% or 50 mol% of TBAF were used instead at 18 °C, the yield of **3aa** fell to 78% and 67%, respectively (Table 1, entries 7 and 8).

Table 1 Optimization of Reaction Conditions for the Direct Vinylogous Aldol Reaction[a]

Entry	Base (mol%)	Solvent	Temp (°C)	Time[b]	Yield (%)[c]	dr (*syn*/*anti*)[d]
1	TBAF(100)	THF	r.t.	22 min	57	97:3
2	TBAF(100)	DMF	r.t.	10 min	57	98:2
3	TBAF(100)	DMSO	r.t.	1 min	59	98:2
4	TBAF(100)	MeCN	r.t.	24 h	44	99:1
5	TBAF(100)	DMSO	18	1.5 min	69	98:2
6	TBAF (90)	DMSO	18	3 min	86	98:2
7	TBAF (80)	DMSO	18	5 min	78	98:2
8	TBAF (50)	DMSO	18	3.5 h	67	98:2

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.5 mmol), aldehyde **2a** (0.65 mmol), and base in solvent (3.0 mL) at r.t. (25 °C) or 18 °C.
[b] Reaction was followed by TLC.
[c] Isolated yields.
[d] Determined by ^{1}H NMR analysis.

Furthermore, we also examined the effect of TMAH, TMAF, and KF on this VA reaction (Table 2). When 30–60 mol% of TMAH (Table 2, entries 1–3) and 50–90 mol% of TMAF (Table 2, entries 4–6) were used instead of TBAF, the reactions proceeded smoothly to give the γ-coupled aldol product **3aa** in moderate yields with a high level of diastereoselectivity. However, the transformation in KF was not achieved due to the low concentration of fluoride ion in DMSO (Table 2, entry 7).

These investigations showed that only the basicity of the fluoride ion or the hydroxide ion is strong enough to abstract a γ-proton directly from β-halo enal **1a** under mild conditions. The exocyclic dienolate **II** produced in situ reacts with an aldehyde at its γ-site to afford intermediate **III**. Subsequent protonation of **III** gives the VA product **3** (Scheme 4).

Based on these important examinations and a plausible reaction pathway as shown above, we selected the polar aprotic solvent DMSO and 90 mol% of TBAF at 18 °C as the optimal reaction conditions to explore the substrate

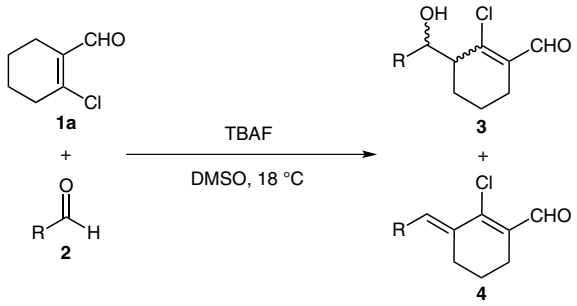
Table 2 The effect of TMAH, TMAF, and KF on Reaction Yield and Selectivity[a]

Entry	Base (mol%)	Solvent	Temp (°C)	Time[b]	Yield (%)[c]	dr (*syn*/*anti*)[d]
1	TMAH (30)	DMSO	18	15 min	47	97:3
2	TMAH (45)	DMSO	18	1 min	58	97:3
3	TMAH (60)	DMSO	18	10 s	31	97:3
4	TMAF (50)	DMSO	18	40 min	45	98:2
5	TMAF (70)	DMSO	18	1 min	61	98:2
6	TMAF (90)	DMSO	18	20 s	52	98:2
7	KF (100)	DMSO	r.t.	48 h	–	–

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.5 mmol), aldehyde **2a** (0.65 mmol), and base in solvent (3.0 mL) at r.t. (25 °C) or 18 °C.
[b] Reaction was followed by TLC.
[c] Isolated yields.
[d] Determined by ^{1}H NMR analysis.

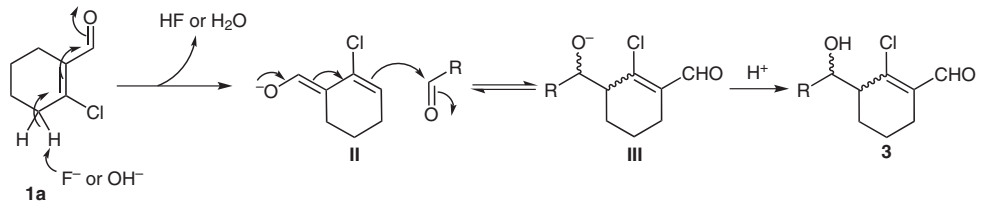
scope for this direct VA reaction. Various aromatic aldehydes and the effects of ring substitution on the product composition and diastereomeric ratio were assessed, low to good yields and high diastereoselectivities were observed for the VA product (Table 3). Substrates with electron-withdrawing groups exhibited much higher reactivity than those with electron-donating groups. Using benzaldehyde **2b** as the electrophilic reagent, the aldol reaction proceeded at a higher temperature, and the corresponding product **3ab** was obtained in a lower yield than the electron-deficient aldehyde **2a**. Unfortunately, the dehydration product **4ab** was also found to form along with the aldol product (Table 3, entry 1). Moreover, the position of the substituents on the aromatic ring had an obvious effect on the product composition and diastereoselectivity. The reactions with electron-deficient aldehydes **2c–i** exclusively afforded aldol products in modest to good yields with high diastereoselectivities (Table 3, entries 2–8). For *para*- and *meta*-substituted benzaldehydes, the *syn*/*anti* ratio was similar to that surveyed in benzaldehyde at 88:12 while the *syn*/*anti* ratio was notably enhanced by *ortho* substituents on the aromatic ring. For a more steri-

Table 3 Direct Vinylogous Aldol Reaction of Cyclic β-Chloro Enal **1a** with Various Aromatic Aldehydes[a]



Entry	R	Time	Yield (%)[b]	Product ratio of **3**/**4**[c]	dr (*syn*/*anti*)[c]
1	**2b**[d] Ph	6 h	30	**3ab/4ab** 83:17	88:12
2	**2c** 2-ClC_6H_4	3 min	81	**3ac/4ac** 100:0	97:3
3	**2d** 2-BrC_6H_4	3 min	81	**3ad/4ad** 100:0	98:2
4	**2e** 2-$O_2NC_6H_4$	3 min	68	**3ae/4ae** 100:0	98:2
5	**2f** 3-$O_2NC_6H_4$	3 min	53	**3af/4af** 100:0	85:15
6	**2g** 4-$O_2NC_6H_4$	2 min	50	**3ag/4ag** 100:0	87:13
7	**2h** 4-$MeO_2SC_6H_4$	5 min	47	**3ah/4ah** 100:0	90:10
8	**2i** 4-ClC_6H_4	22 min	41	**3ai/4ai** 100:0	87:13
9	**2j**[e] 4-FC_6H_4	6 h	20	**3aj/4aj** 68:32	83:17
10	**2k**[d] 2-naphthyl	6 h	26	**3ak/4ak** 73:27	97:3
11	**2l** 2-furyl	30 min	55	**3al/4al** 97:3	80:20
12	**2m** 3,4-$(MeO)_2C_6H_3$	12 h	–	–	–

[a] Unless otherwise noted, reactions were performed on a 0.50 mmol scale of **1a** using 0.65 mmol of **2** and 90 mol% TBAF in 3.0 mL DMSO.
[b] Yields of isolated product.
[c] Determined by ^{1}H NMR analysis.
[d] Reaction performed at 28 °C.
[e] Reaction performed at 32 °C.



Scheme 4 Proposed pathway for the direct VA reaction

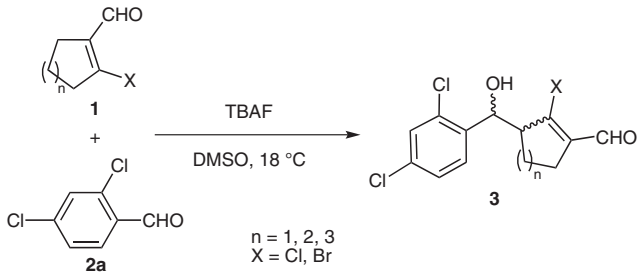
cally demanding bromine or nitro group as *ortho* substituent, the *syn*/*anti* ratio increased to 98:2 (Table 3, entries 3 and 4). The low reactivity of **2j** or **2k** was circumvented by increasing the temperature and prolonging the reaction time (Table 3, entries 9 and 10). However, the reactions gave the mixtures of aldol and dehydration products in relative low yields with high diastereoselectivities. 2-Napthylaldehyde (**2k**) provided an obvious improvement in the *syn*/*anti* ratio over that examined in benzaldehyde, similar to the described *ortho*-substitution effect. The heteroaromatic 2-furaldehyde (**2l**), where the furan ring was spatially less demanding and more electron-rich than the phenyl ring, caused a drop in *syn*/*anti* ratio and generated a trace dehydration product **4al** (Table 3, entry 11). Aldehyde **2m** failed to give the desired product due to its unreactivity under the reaction conditions (Table 3, entry 12).

In addition, various cyclic β-haloenals **1b–e** were also investigated (Table 4). In the reaction of cyclic β-bromide enal **1b**, modest yield and high diastereoselectivity were observed for the aldol product **3ba**. The increase in *syn* selectivity was presumably due to the bromine atom being larger than the chlorine atom, and, more likely, the reason for the decrease in the yield was the reduced electronegativity of the bromine atom (Table 4, entry 2). The five-membered enals **1c** and **1d** could be smoothly converted into the desired products in modest yields with significantly reduced diastereoselectivities, whereas the seven-membered enal **1e** was inactive, and no desired product was detected (Table 4, entries 3–5). The results showed that the reaction rates were related to the structural effects of these generated dienolates in situ,[13] and the six-membered dienolates exhibited the highest reactivities and diastereoselectivities in the VA reaction.

The above results indicated that the high regioselectivity of nucleophilic addition for these exocyclic dienolates are strongly dependent on the different kind of electrophilic reagents. Obviously, TBAF containing a rather large tetrabutylammonium cation also tends to favor the formation of the homoallylic alcohol **3** when an aromatic aldehyde was used as electrophile.

The stereochemical outcome can be explained by examining possible transition states from the Newman projections **IV** and **V** (Figure 2). It is clear that when cyclic β-halo enal was used as dienolate equivalents, the transition state (TS) for conformer **IV** has fewer steric interactions than that of the TS for conformer **V**, affording predominantly the *syn* product instead of the *anti* product. Nonbonding steric interactions between substituted aromatic ring and the X (Cl or Br) atoms would increase in the proposed TS conformer **V**. Additionally, for *ortho*-, *para*-, and *meta*-substituted benzaldehydes, the *ortho*-substituted aromatic rings show increased preference for the *syn* adducts. For instance, when Cl, Br or NO_2 as the *ortho* substituent is present on the benzene ring (Table 3, entries 2–4), the *syn*-selectivity ratio is improved markedly to 97:3 and 98:2, respectively, presumably owing to the additional steric demands of the *ortho* substituents.

Table 4 Direct Vinylogous Aldol Reaction of Various Cyclic β-Haloenals with 2,4-Dichloroaldehyde[a]



Entry	n	X	Time	Product **3** Yield (%)[b]		dr (*syn*/*anti*)[c]
1	2	Cl	3 min	**3aa**	86	98:2
2	2	Br	12 min	**3ba**	67	99:1
3	1	Cl	5 min	**3ca**	62	78:22
4	1	Br	26 min	**3da**	45	79:21
5	3	Cl	24 h	–	–	–

[a] Unless otherwise indicated, reactions were performed on a 0.50 mmol scale of **1** using 0.65 mmol of **2a** and 90 mol% TBAF in 3.0 mL DMSO.
[b] Yields of isolated product.
[c] Determined by ^{1}H NMR analysis.

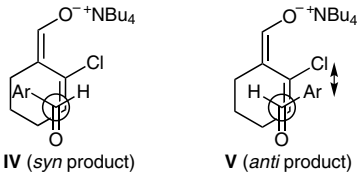


Figure 2 The Newman projections of possible transition-state conformers **IV** and **V**

In conclusion, we have developed a direct vinylogous aldol addition of cyclic β-halo enals with aromatic aldehydes initiated with TBAF as a key reagent. The reaction

is carried out under mild conditions, and the operation is simple and practical. This unprecedented chemical transformation affords highly functionalized homoallylic alcohols having two stereocenters at the γ- and δ-positions with a high diastereomeric ratio, which can be easily transformed into other useful building blocks and are also synthetically attractive in biological active molecules. Current efforts focus on expanding the scope of the vinylogous donors and acceptors as well as exploring the applications of the homoallylic alcohols in organic synthesis, and the results will be reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are experimental procedures, analysis of NMR spectra of homoallylic alcohols **3**, and crystal data for compound *syn*-**3aa**.

Acknowledgment

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